Copper-catalyzed, oxidative sp^2 C-H cyanation: facile synthesis of aromatic carbonitriles

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DOI: http://dx.doi.org/10.3998/ark.5550190.p008.682

Abstract

$Cu(OAc)_2$-catalyzed regioselective oxidative C-H cyanation of two different types of aromatics was described, providing facile access to functionalized heterocycles in good yields. Control experiments suggest the copper chelation-assisted oxidative C-H activation mechanism.

Keywords: C-H activation, cyanation, copper catalyzed, aryl carbonitriles

Introduction

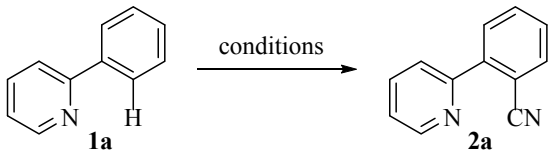
Aryl carbonitriles are versatile building blocks in organic synthesis for pharmaceuticals, natural products, dyes, agrochemicals and materials. Moreover, the nitrile moiety also serves as a key role during the transformations into the formation of amines, amides, acids/ester, ketones, aldehydes and heterocycles.[1] Typical strategies for the synthesis of aryl nitriles involve the Rosenmund-von Braun,[2-3] Sandmeyer,[4] and Schmidt[5] reactions. Recent advances show that the cross-coupling between aryl (pseudo)halides and various cyanide sources such as NaCN,[6] KCN,[7] CuCN,[8] TMSCN,[9] $Zn(CN)_2$,[10] ethyl cyanoacetate,[11] DMF,[12] CH_3CN,[13] $HCONH_2$,[14] benzyl cyanide,[15] alcohols,[16] $MeNO_2$[17] and acetone cyanohydrin[18] is also an alternative way to aryl nitriles. Furthermore, metal-catalyzed direct cyanation of aromatic C-H bonds has emerged as a useful alternative, owing to its potential atom- and step-efficient advance. Yu *et al*. first disclosed the cyanation of C-H bonds of 2-arylpyridine with $Cu(OAc)_2$/TMSCN($MeNO_2$)/O_2.[17] Following this pioneering report, there has been an increase of activity in this area with various catalytic systems. Cheng reported Pd-catalyzed cyanation of 2-arylpyridine C-H bond with CuCN[19] and a cascade bromination/cyanation reaction using $K_3[Fe(CN)_6]$.[20] $K_4[Fe(CN)_6]$ also

proved to be a useful CN source in Pd catalyzed cyanation reactions.[21] Recently, the research groups of Chang[22] and Jiao[23] found Pd/DMF with/without NH_3 was efficient system for C-H cyanation. Meanwhile, Cheng found DMSO contributes to the formation of final nitrile.[24] Very recently, Zhu[25] and Xu[26] communicated the cyanation of C-H using a Pd/isocyanide system. Pd-free examples of C-H cyanation are comparatively few. In particular, the less expensive copper-catalyzed examples are limited. After Yu's report mentioned above, recently Wang *et al.* communicated the CuBr/benzyl nitrile/DMF system for cyanation of 2-phenylpyridines.[27] Daugulis *et al.* investigated the direct cyanation of benzothiazole.[28] Chang's group disclosed copper-mediated cyanation of electron-rich benzenes,[29] indoles[30] and 2-phenylpyridines[30] with NH_4I and DMF. Very recently, Fan *et al.* have found that $Cu(OAc)_2$/AIBN is also an efficient system for the cyanation of aromatics.[31] These copper-catalyzed approaches on cyanation still leave much scope to develop for the direct cyanation of other important structures. Herein, we report a straight Cu-catalyzed regioselective C(sp^2)-H cyanation of 2-arylpyridines as well as pyrazoles, which are important units and blocks due to their pharmaceutical or biological activity and facile derivatization.[32]

Results and Discussion

Initially, we examined whether 2-phenylpyridine (**1a**) could undergo cyanation under CuCN/air/DMF system at 120 ^oC (similar to Wang's procedure[27]). However, no conversion of the starting substrates **1a** was observed (Table 1, entry 1). Yu demonstrated that $Cu(OAc)_2/O_2$ worked in the oxidative C-H functionalization.[17] We envisioned that one of the oxidants could work. To test our hypothesis, we employed O_2 as the sole oxidant for the cyanation. However, O_2 alone gave no conversion of raw materials (Table 1, entry 2), and the same situation was true for $Cu(OAc)_2$ (Table 1, entry 3) while trace product was seen with combined $Cu(OAc)_2$ and O_2 (Table 1, entry 4). Further improvement with the introduction of anhydrous CuBr (0.2 equiv.) was achieved with an increased yield to 8% (Table 1, entry 5), which meant that *in situ* bromination might occur during the reaction, albeit relative low yield. To test our hypothesis, we introduced water (5.0 equiv.) into the reaction and the result showed that no conversion of **1a** was found (Table 1, entry 6), which meant that water could sharply inhibit the reaction. However, without $Cu(OAc)_2$, CuBr alone could not catalyze the reaction (Table 1, entry 7). Replacing CuBr with KI led to an accelerated reaction and resulted in a significantly improved yield.[33] Our experiments confirmed the catalysis by KI (Table 1, entry 8). Finally, the combination of $Cu(OAc)_2$ and KI (0.1 equiv.) gave the desired **2a** in moderate yield and chemoselectivity (Table 1, entry 8). There was no difference between iodide ion sources (Table 1, entries 8, 9). Further addition of 10 equiv. AcOH made a great improvement and gave the desired product in good yield and chemoselectivity (Table 1, entry 10).

Table 1. Optimization of the cyanation of 2-phenylpyridine[a]



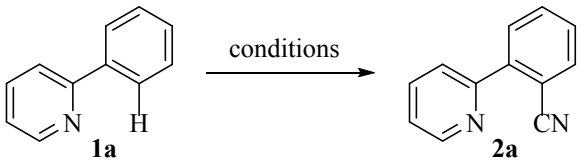
Entry	Oxidant	Additive	Yield/%[b]
1	Air	-	0
2	O_2	-	0
3	$Cu(OAc)_2$	-	0
4	$Cu(OAc)_2/O_2$	-	2
5	$Cu(OAc)_2$	CuBr (0.2 equiv)	8
6	$Cu(OAc)_2$	H_2O (5.0 equiv)	0
7	CuBr (1.2 equiv)	-	0
8	$Cu(OAc)_2$	KI (0.1 equiv)	35
9	$Cu(OAc)_2$	CuI (0.1 equiv)	34
10	**$Cu(OAc)_2$**	**KI (0.1 equiv), AcOH (10 equiv)**	**72**

[a.] Unless otherwise noted, reaction conditions: substrate (0.2 mmol, 1.0 equiv), CuCN (0.3 mmol, 1.5 equiv), $Cu(OAc)_2$ (0.24 mmol, 1.2 equiv), anhydrous DMF (2.0 mL) stirred at 120 ^oC under N_2 atmosphere for 36 h. [b.] Isolated yield.

Further experiments with other cyano sources such as TMSCN, $K_4[Fe(CN)_6]$ and $Zn(CN)_2$, even with $Cu(OAc)_2$ and KI, confirmed our choice of CuCN (Table 2, entries 1-4). Subsequently, several other oxidants ($CuBr_2$, $Cu(NO_3)_2$, CuO, $CuSO_4$, Oxone, $Fe(NO_3)_3$) were also tested (Table 2, entries 5-10). None of them was effective in the cyanation of compound **1a**. Finally, the solvent was screened and the results showed that the reaction in DMSO, NMP and DMA gave results competitive with DMF, while other solvents such as CH_3CN, toluene, AcOH and octanol proved to be ineffective (Table 2, entries 11-17). DMF was chosen for its facile handling and commercial availability. Herein, $Cu(OAc)_2$/CuCN /DMF system was confirmed as the optimal conditions for cyanation of 2-phenylpyridines, which could gave a higher yield than reported results.[17]

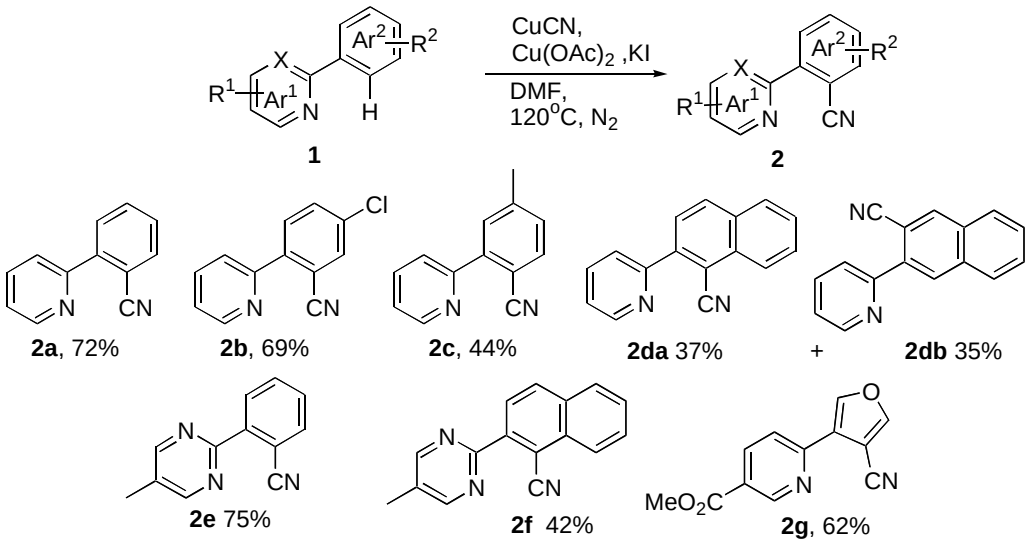
With the optimal conditions in hand, the scope and limitation of the reaction were investigated and the results were collected in Scheme 1. As to four reported products (**2a**-**2d**), our cyanation condition gave comparable (**2c**) or higher yields (**2a**, **2b** and **2d**). Replacing the directing group with 5-methylpyrimidine, 2-(5-methylpyrimidin-2-yl)benzonitrile (**2e**) could be generated in good yield and the more electron-deficient product **2f** could be obtained in moderate yield. Finally, methyl 6-(furan-3-yl)nicotinate could be applied in this reaction producing the corresponding **2g** in good yield.

Table 2. Optimization of the cyano source, oxidant and solvent [a]



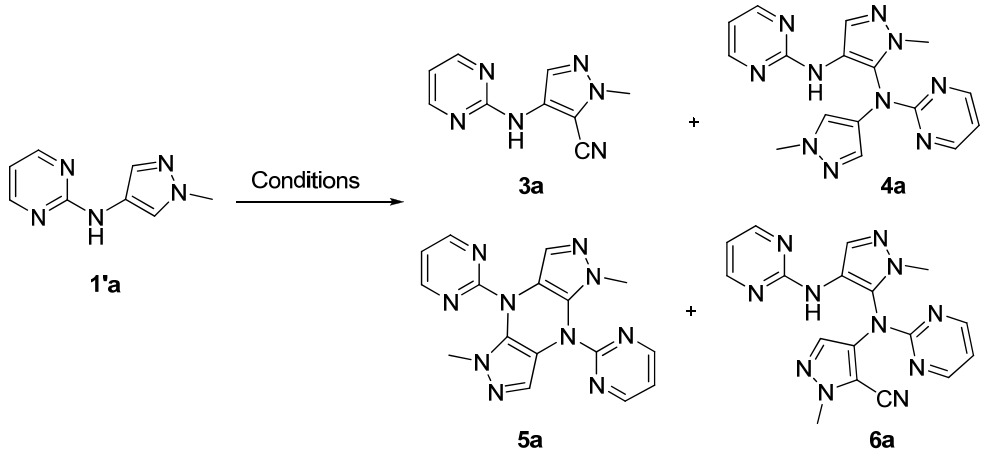
Entry	Cyano source	Oxidant	Solvent	Yield/% [b]
1	CuCN	$Cu(OAc)_2$	DMF	72
2	TMSCN	$Cu(OAc)_2$	DMF	20
3	$K_4[Fe(CN)_6]$	$Cu(OAc)_2$	DMF	28
4	$Zn(CN)_2$	$Cu(OAc)_2$	DMF	4
5	CuCN	$CuBr_2$	DMF	0
6	CuCN	$Cu(NO_3)_2$	DMF	0
7	CuCN	CuO	DMF	0
8	CuCN	$CuSO_4$	DMF	0
9	CuCN	Oxone	DMF	0
10	CuCN	$Fe(NO_3)_3$	DMF	0
11	CuCN	$Cu(OAc)_2$	AcOH	0
12	CuCN	$Cu(OAc)_2$	DMSO	70
13	CuCN	$Cu(OAc)_2$	NMP	65
14	CuCN	$Cu(OAc)_2$	CH_3CN	0
15	CuCN	$Cu(OAc)_2$	Toluene	0
16	CuCN	$Cu(OAc)_2$	DMA	68
17	CuCN	$Cu(OAc)_2$	Octanol	0

[a.] Reaction conditions: substrate **1a** (0.2 mmol, 1.0 equiv), cyano source (0.3 mmol, 1.5 equiv), oxidant (0.24 mmol, 1.2 equiv), anhydrous DMF (2.0 mL) and KI (0.02 mmol 0.1 equiv) stirred at 120 ^oC under N_2 atmosphere for 36 h. [b.] Isolated yield.

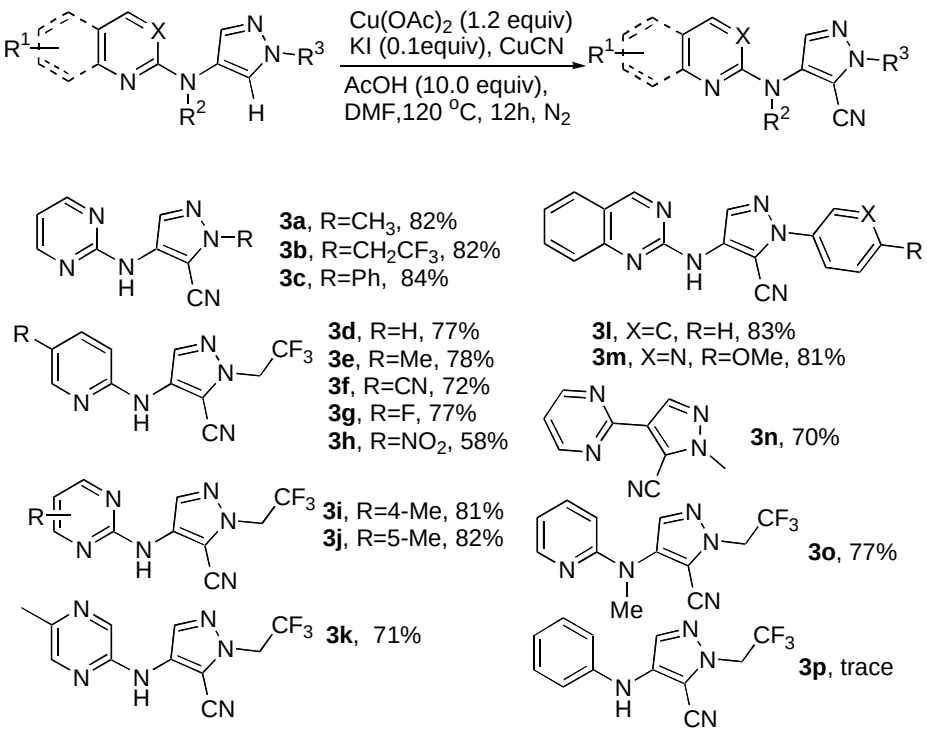


Scheme 1. Scope of the cyanation of 2-arylpyridines.

Due to the wide usage of pyrazoles in pharmaceuticals, *N*-(1-methyl-1*H*-pyrazol-4-yl)pyrimidin-2-amine **1′a** was tried as a model substrate. Under standard conditions, the desired cyanated product **3a** was obtained in 82% yield during 12 hrs, which meant a rapid reaction under these conditions. It is worthy of mention that, in the absence of acetic acid, **1′a** afforded the desired cyanated product **3a** with intermolecular coupling product **4a** and amination product **6a**. Fortunately, the byproducts could be inhibited with the addition of 10 equivalents of AcOH (Scheme 2).



Scheme 2. Cyanation of **1′a** under different conditions: without acetic acid: **3a**:**4a**:**6a**=56:25:10; with acetic acid **3a**:**4a**:**6a**=92:1:0.



Scheme 3. Scope of the cyanation of substituted pyrazoles.

Under these conditions, we explored the scope and limitation the cyanation of different pyrazoles (Scheme 3). Pyrazoles with Me, CH_2CF_3 and Ph at the 1 position were cyanated smoothly in 82%, 82% and 84% yields, respectively (**3a**, **3b** and **3c**, Scheme **3**). These results suggested that the cyanation was not sensitive to the electronic character of the substituent at the 1 position of pyrazole, while 4- and 5-methylpyrimidines led to similar results, producing **3i** and **3j** in 81% and 82% yields. Substituents with varied electronic properties, such as H (**3d**), methyl (**3e**), fluoro (**3g**), cyano (**3f**) and nitro (**3h**), on the 5-position of the pyridine ring were tolerated under the reaction conditions, giving comparable or slightly lower yields. Other heterocycle-substituted 4-aminopyrazoles including 5-methylpyrazin-2-yl (**3k**), quinazolin-2-yl (**3l** and **3m**) were successfully applied in this reaction with comparable yields. Interestingly, the formation of 1-methyl-4-pyrimidin-2-yl-5-cyanopyrazole (**3n**) demonstrated that the 4-amino in the pyrazoles was not crucial. This result was further verified by the methyl substitution of the 4-amino group (**3o**). Compounds **3d** and **3o** were obtained in the same yield. However, the 4-(*N*-phenylamino) substituted pyrazole (**3p**) failed to yield the desired product, which meant that the directing group was crucial.

The regioselectivity of the C-H cyanation was confirmed by Noesy analysis of **3b** and X-ray analysis of **3e** (Figure 1).[34] The results confirmed that the cyanation occurred at the 5 position of the pyrazole.

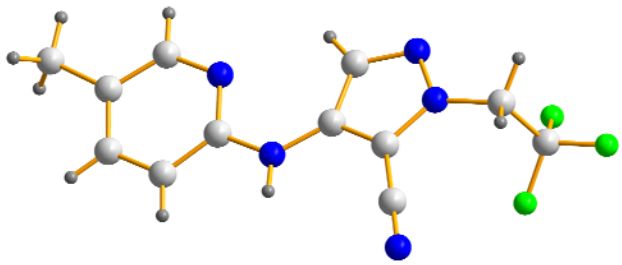
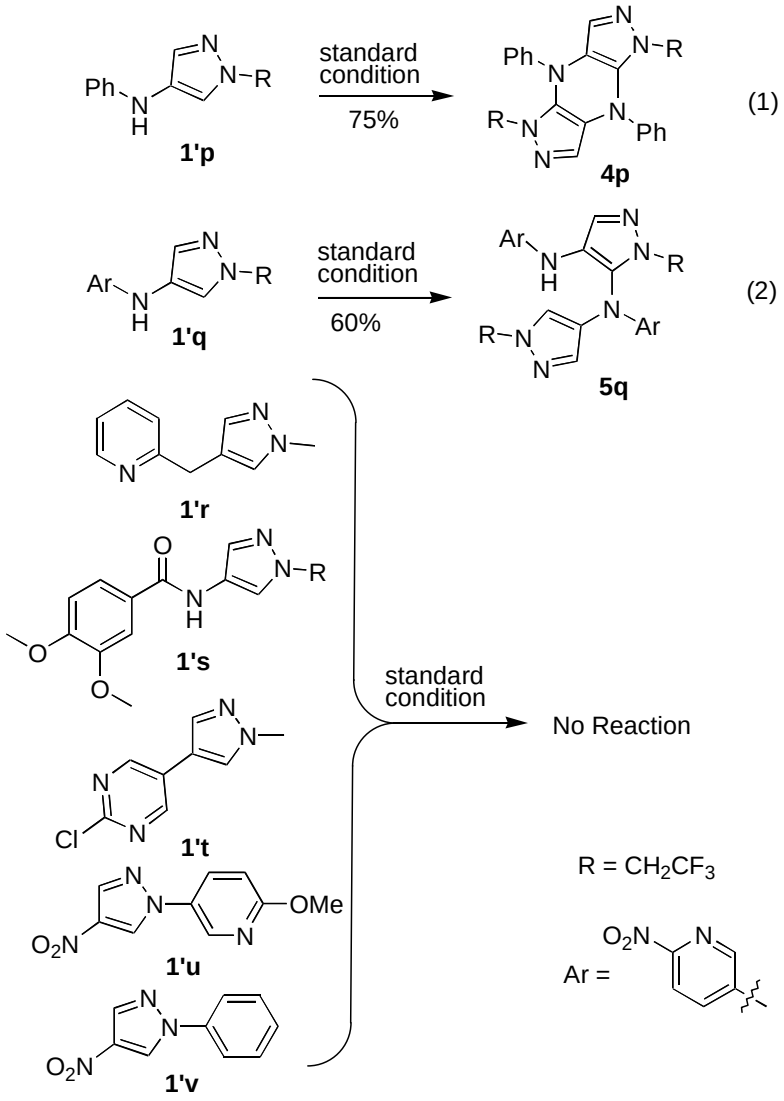


Figure 1. X-ray structure of **3e.**

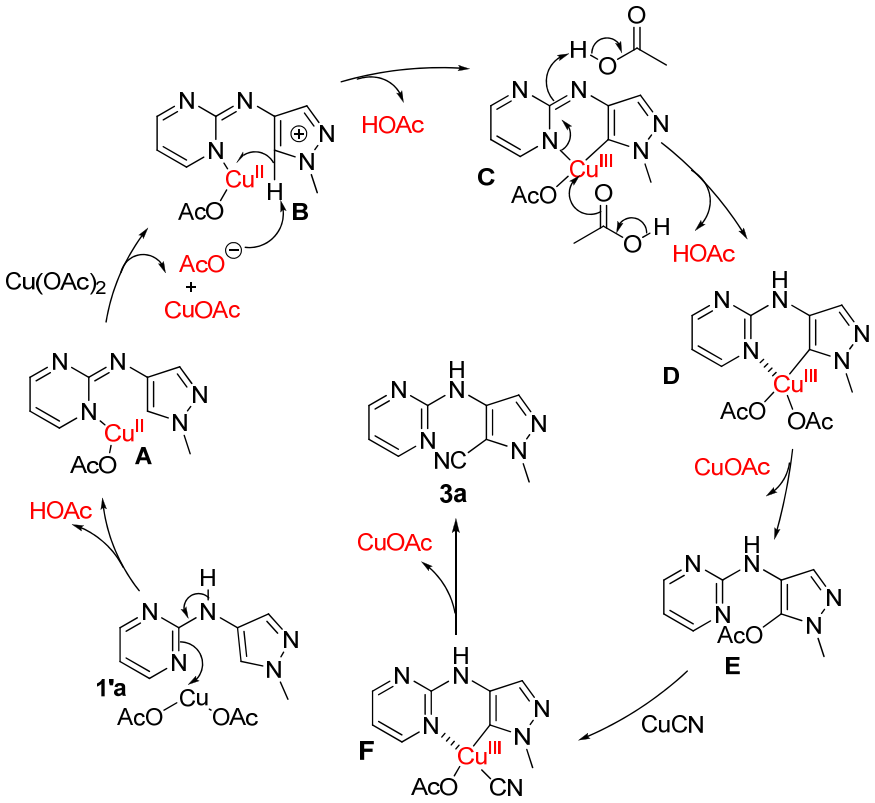
To further understand the reaction, mechanistic studies were also carried out (Scheme 4). First, control experiments were performed. Under the optimal conditions, the relative higher nucleophile 4-phenylaminopyrazole **1′p** produced the corresponding double C-H amination product **4p** in 75% yield (eq 1), whereas **1′q** gave the mono C-H amination product **5q** in 60% yield (eq 2). These results demonstrated that amination and cyanation at the 5-position of pyrazole were competitive reactions. Inserting a methylene into the 4-position of pyrazole and pyrimidine, **1′r** did not yield any corresponding product. The same situation was found in the amide group **1′s**. A directing group effect was further confirmed with 4-(2-chloropyrimidine-5-yl)pyrazole **1′t**, which afforded no desired product. Reactions of nitro-substituted pyrazoles, either **1′u** or **1′v**, which are highly electron-deficient aromatics, were sluggish, and no product was obtained.



Scheme 4. Mechanistic studies.

Based on the reactions above and the substrates, conclusions could be drawn as follows:
1) the $Cu(OAc)_2$ is essential to the reaction and the OAc anion should participate in the reaction;
2) the copper(II) ion participates in the reaction through chelation with the *N*-amino *N*-heterocycle;
3) KI participates in the reaction and accelerates the reaction.
Zhou *et al.* have demonstrated that the chelation of copper with *N*-heterocycles was the initial reaction.[35] Single electron transfer (SET) is thought to be the reasonable mechanism with literatures. Thus, we envisioned the cyanation reaction proceeded with copper chelation-assisted six-membered cyclic process as shown in Scheme 5. Oxidative addition of compound **1'a** with $Cu(OAc)_2$ results in the formation of intermediate **A**, which reacts with another $Cu(OAc)_2$ via SET to give intermediate **B** with the release of AcO^-. Oxidation of intermediate **B** leads to the

Cu(III) intermediate **C**, which reacts with AcOH to give intermediate **D**. Reductive elimination of intermediate **D** gives the intermediate **E**, which reacts with CuCN to give the key intermediate Cu(III) compound **F**. The final product **3a** is obtained from the reductive elimination of intermediate **F**.



Scheme 5. Proposed mechanism.

Conclusions

In conclusion, we have described the direct C-H cyanation with CuCN/$Cu(OAc)_2$ to form aromatic carbonitriles. The present approach is convenient with easy operation, inexpensive catalytic system and broad substrate scope. In addition, a plausible mechanism is proposed to account for the formation of products. Further experiments are currently underway in our lab.

Experimental Section

General. Organic solutions were concentrated by rotary evaporation (house vacuum, ~25 Torr) at 23-30 °C. Flash column chromatography was performed by employing silica gel (60 Å pore size, 230-400 mesh, standard grade). Analytical thin layer chromatography (TLC) was performed

using aluminum plates pre-coated with silica gel (0.25 mm, 60 Å pore size, 230-400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 mm). TLC plates were visualized by exposure to ultraviolet light (UV) and/or exposure to phosphmolybdic acid (PMA) followed by heating on a hot plate. Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded with Varian Mercury 400 (400 MHz/ 100 MHz) NMR spectrometers. Chemical shifts for protons are reported in parts per million (δ scale) and internally referenced to the tetramethylsilane signal. Chemical shifts for carbon are reported in parts per million (δ scale) and referenced to the carbon resonances of the solvent ($CDCl_3$: δ 77.36, the middle peak). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet, dt = double triplet, td = triple doublet), coupling constant in Hz, and integration. Liquid chromatography mass spectra were obtained using an Agilent Technologies 6120MSD mass spectrometer.

Typical procedure for the cyanation of aromatics. To anhydrous *N*,*N*-dimethylformamide (2 mL) was added *N*-heterocycles **1** (0.2 mmol, 1.0 equiv), CuCN (0.3 mmol, 1.5 equiv), $Cu(OAc)_2$ (0.24 mmol, 1.2 equiv), AcOH (2.0 mmol, 10 equiv) and KI (0.02 mmol, 0.1 equiv) under N_2 atmosphere. The reaction mixture was warmed to 120 ^oC and kept for 12 hrs. After the completion of the reaction, the reaction mixture was directly purified with flash chromatography (MeOH/water = 1:10 ~ 10:1) and the desired product was obtained.

Preparation of substrates

Typical procedure A. Aminopyrazole (3.0 mmol, 1.0 equiv), halide (3.15mmol, 1.05 equiv) and TsOH (3.0 mmol, 1.0 equiv) were added to 2-propanol (10 mL). The resultant mixture was reacted under microwave radiation at 145 ^oC for 1hrs. On the completion of the reaction, the solvent was removed under reduced pressure. To the residue was added water (50 mL), neutralized with saturated aqueous $NaHCO_3$, extracted with ethyl acetate. The combined organic phase was successively washed with water, brine for three times and dried over Na_2SO_4. After the removal of the solvent, purification of the residue with flash chromatography ($MeOH/H_2O$ = 0:1~10:1) gave the desired product.

Typical procedure B. To 1,4-dioxane (15 mL) and water (1 mL) was added bromopyrimidine (3 mmol, 1.0 equiv), pyrazole boric acid ester (3.6 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (0.3 mmol, 1.0 eq) and K_2CO_3 (6 mmol, 2.0 eq) under N_2 atmosphere. The reaction mixture was warmed to 110 ^oC and kept overnight. After the completion of the reaction, the content was poured into water (100 mL) and extracted with ethyl acetate. The combined organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Desired product was obtained after purification with flash chromatography (Petro-Ester (PE)/EtOAc = 1:0~1:1).

Typical procedure C. To dichloromethane (15 mL) was added aminopyrazole (5 mmol, 1.0 equiv), phenyl boric acid (7.5 mmol, 1.5 equiv), $Cu(OAc)_2$ (10 mmol, 2.0 equiv) and anhydrous pyridine (50 mmol, 10.0 equiv) under O_2 atmosphere. The reaction mixture was heated to reflux and kept for 48 hrs. After the completion of the reaction, the solvent was evaporated under

reduced pressure. The residue was purified with flash chromatography (PE/EtOAc = 1:0~3:1) to generate the desired product.

Typical procedure D. To 1,4-dioxane (15 mL) and water (1 mL) mixture were added bromopyridine (3 mmol, 1.0 equiv), substituted pyrazole (3.6 mmol, 1.2 equiv), $Pd(dppf)Cl_2$ (0.3 mmol, 1.0 equiv) and Cs_2CO_3 (6 mmol, 2.0 equiv) under N_2 atmosphere. The reaction mixture was warmed to 110 ^oC and kept overnight. After the completion of the reaction, the content was poured into water (100 mL) and extracted with ethyl acetate. The combined organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Desired product was obtained after purification with flash chromatography (PE/EtOAc = 1:0~1:1).

Typical procedure E. To pyrazole (3 mmol, 1.0 equiv) and Et_3N (4.5 mmol, 1.5 equiv) dissolved in dichloromethane (15 mL) was added acyl chloride (3.15 mmol, 1.05 equiv) in an ice-water bath. After the completion of addition, the resultant reaction mixture was warmed to room temperature and kept for 2hrs. On the completion of the reaction, the solvent of the reaction mixture was removed under reduced pressure. The residue was poured into water (50 mL) and the desired product was obtained.

For the synthesis of *N*-aryl substituted pyrazoles, procedure F. Nitropyrazoles (10 mmol, 1.1 equiv), aryl halide (9.1 mmol, 1.0 equiv), CuI (1.0 mmol, 0.1 equiv) and K_2CO_3 (18.2 mmol, 2.0 equiv) were added to DMF (20 mL) under N_2 atmosphere. The resultant mixture was heated to 110 ^oC and kept overnight. On the completion of the reaction, the reaction mixture was poured into water, and extracted with ethyl acetate. The combined organic phase was successively washed with water, brine for three times and dried over Na_2SO_4. After the removal of the solvent, purification of the residue with flash chromatography (PE/EtOAc = 40:1~1:1) gave the desired product.

Typical procedure G. To 1,4-dioxane (15 mL) were added chloro-substituted N-heterocycles (10.0 mmol), aromatic boronic acid (or pinacol ester, 12.0 mmol), $Pd(dppf)Cl_2$ (0.73 g, 1.0 mmol) and aqueous Cs_2CO_3 (2 N, 10 mL, 20.0 mmol) under N_2 atmosphere. The content was heated and kept at 110 ^oC overnight. The reaction mixture was cooled to room temperature after the completion of the reaction. Dioxane was removed under reduced pressure. The resultant aqueous solution was extracted with EtOAc. The combined organic phase was washed with water and saturated brine for three times, and dried over Na_2SO_4. After the removal of the solvent under reduced pressure, the residue was charged to flash chromatography, which gave the pure product.

2-Phenylpyridine (1a). Procedure **G**. Phenylboronic acid was used. Colorless oil, 78%; ^1H NMR (400 MHz, $CDCl_3$): δ 8.69-8.70 (m, 1H), 7.99–8.01 (m, 2H), 7.70–7.74 (m, 2H), 7.45-7.49 (m, 2H), 7.39–7.42 (m, 1H), 7.19-7.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 149.5, 139.3, 136.8, 129.0, 128.7, 126.9, 122.1, 120.5. LC-MS (ESI *m/z*) 156.0 $[M+H]^+$; It was in agreement with literature.[36]

2-(4-Chlorophenyl)pyridine (1b). Procedure **G**. 4-Chlorophenylboronic acid was used. White solid, mp 52-53°C (lit.[37] 51-52°C) 70%;^1H NMR (400 MHz, $CDCl_3$): δ 8.66-8.68 (m, 1H), 7.91-7.95 (m, 2H), 7.66-7.75 (m, 2H), 7.41–7.43 (m, 2H), 7.20-7.23 (m, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 156.1, 149.6, 137.7, 136.9, 135.2, 128.9, 128.2, 122.3, 120.3; LC-MS (ESI *m/z*) 189.9 $[M+H]^+$. It was in agreement with literature.[37]

2-(3-Methylphenyl)pyridine (1c). Procedure **G**. 3-Methylphenylboronic acid was used. White solid, mp 84-85 °C (lit.[38] 80-85 °C) 65%; ^1H NMR (400 MHz, $CDCl_3$): δ 8.68-8.69 (m, 1H), 7.84-7.85 (m, 1H), 7.75-7.77 (m, 1H), 7.68-7.71 (m, 2H), 7.33-7.37 (m, 1H), 7.17–7.25 (m, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 149.5, 139.3, 138.4, 136.7, 129.7, 128.6, 127.6, 124.0, 121.9, 120.6, 21.5; LC-MS (ESI *m/z*) 170.0 $[M+H]^+$. It was in agreement with literature.[38]

2-(Naphthalen-2-yl)pyridine (1d). Procedure **G**. 2-Naphthaleneboronic acid was used. White solid, mp 78.5-79 °C (lit.[39] 78.0-78.5 °C) 70%; ^1H NMR (400 MHz, $CDCl_3$): δ 8.74-8.76 (m, 1H), 8.49 (s, 1H), 8.14-8.16 (m, 1H), 7.93-.93 (m, 2H), 7.84-7.86 (m, 2H), 7.73-7.78 (m, 1H), 7.48-7.52 (m, 2H), 7.22-7.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 149.6, 136.9, 136.5, 133.7, 133.5, 128.7, 128.4, 127.6, 126.5, 126.4, 126.7, 124.5, 122.1, 120.8; LC-MS (ESI *m/z*) 206.0 $[M+H]^+$. It was in agreement with literature.[39]

5-Methyl-2-(phenyl)pyrimidine (1e). Procedure **G**. Phenylboronic acid was used. White solid, mp 68-69 °C (lit.[40] 69 °C) 74%; ^1H NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 2H), 8.39-8.41 (m, 2H), 7.43-7.49 (m, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4, 157.3, 137.5, 130.3, 128.5, 128.2, 127.9, 15.4; LC-MS (ESI *m/z*) 171.0 $[M+H]^+$. It was in agreement with literature.[40]

5-Methyl-2-(naphthalen-2-yl)pyrimidine (1f). Procedure **G**. 2-Naphthalene-boronic acid was used. White solid, mp 197.6-198.4 °C, 61%; ^1H NMR (400 MHz, $CDCl_3$): δ 8.95 (s, 1H), 8.66 (s, 2H), 8.50-8.53 (m, 1H), 7.97-7.99 (m, 1H), 7.92-7.94 (m, 1H), 7.85-7.87 (m, 1H), 7.48-7.53 (m, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3, 157.4, 134.7, 134.6, 133.3, 129.1, 128.3, 128.2, 128.1, 127.6, 127.0, 126.2, 124.9, 15.4; LC-MS (ESI *m/z*) 221.0 $[M+H]^+$. Calcd for: $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72%; found: C, 81.13; H, 5.87; N, 12.58%.

Methyl 6-(furan-3-yl)nicotinate (1g). Procedure **G**. 3-Furanboronic acid pinacol ester was used. Gray solid, mp 154.3-156.2 °C, 83%; ^1H NMR (400 MHz, $CDCl_3$): δ 9.15 (s, 1H), 8.24 (d, *J* 8.1, 1H), 8.10 (s, 1H), 7.48-7.50 (m, 2H), 6.91 (s, 1H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 155.3, 150.9, 144.2, 142.7, 137.8, 126.4, 123.8, 119.3, 108.6, 52.2; LC-MS (ESI *m/z*) 203.9 $[M+H]^+$. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89%; found: C, 65.35; H, 4.69; N, 6.78%.

***N*-(1-Methyl-1*H*-pyrazol-4-yl)pyrimidin-2-amine (1′a).** Procedure **A**, light yellow solid, 76%, mp 147.2-147.9 °C; ^1H NMR (400 MHz, DMSO): δ 9.38 (s, 1H), 8.37 (d, *J* 4.6Hz, 2H), 7.87 (s, 1H), 7.45 (s, 1H), 6.67 (t, *J* 4.6Hz, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 160.0, 158.5, 130.3, 123.6, 120.9, 123.6, 120.9, 111.4, 39.1; LC-MS (ESI *m/z*) = 176.0 $[M+1]^+$. Calcd for $C_8H_9N_5$: C, 54.85; H, 5.18; N, 39.98%; found: C, 54.67; H, 5.25; N, 39.83%.

***N*-(1-(2,2,2-Trifluoroethyl)-1*H*-pyrazol-4-yl)pyrimidin-2-amine (1′b).** Procedure **A**, light yellow solid, 84%, mp 174.3-175.1°C; ^1H NMR (400 MHz, DMSO): δ 9.54 (s, 1H), 8.41 (d, *J* 4.8Hz, 2H), 8.08 (s, 1H), 7.62 (s, 1H), 6.72 (t, *J* 4.8Hz, 1H), 5.03 - 5.10 (m, 2H); ^{13}C NMR (100 MHz, DMSO): δ 159.9, 158.5, 132.5, 125.6, 124.5, 122.8, 121.3, 111.8, 51.8; LC-MS (ESI) =

243.9 $[M+1]^+$. Calcd for $C_9H_8F_3N_5$: C, 44.45; H, 3.32; N, 28.80%; found: C, 44.32; H, 3.58; N, 28.67%.

***N*-(1-Phenyl-1*H*-pyrazol-4-yl)pyrimidin-2-amine (1′c).** The reduction of 4-nitro-1-phenyl-1*H*-pyrazole was carried out under the catalysis of Pd/C with H_2 in methanol. 4-Nitro-1-phenyl-1*H*-pyrazole (0.57 g, 3.0 mmol) and Pd/C (0.1 g) was added into methanol (10mL). The atmosphere was exchanged with H_2 three times. The reaction was kept for 3hrs at room temperature. On the completion of the reaction, the catalyst Pd/C was filtered off and the solvent was removed under reduced pressure. 1-Phenyl-1*H*-pyrazol-4-amine was obtained as a gray solid (0.53g). LC-MS (ESI) = 160.1 $[M+1]^+$. The reaction of 1-phenyl-1*H*-pyrazol-4-amine and 2-chloropyrimidine under procedure **A** generated **1′c** as a white solid with 68% yield. mp 164.8-165.7 ^oC; ^1H NMR (400 MHz, DMSO): δ 9.60 (s, 1H), 8.55 (s, 1H), 8.45 (d, *J* 4.7Hz, 2H), 7.81 (s, 1H), 7.75 (d, *J* 7.9Hz, 2H), 7.46 (t, *J* 7.8Hz, 2H), 7.24 (t, *J* 7.3Hz, 1H), 6.75 (t, *J* 4.7Hz, 1H); ^{13}C NMR (100 MHz, DMSO): δ 159.9, 158.6, 140.3, 133.7, 129.9, 126.1, 125.9, 118.2, 116.7, 112.0; LC-MS (ESI) = 238.0 $[M+1]^+$. Calcd for $C_{13}H_{11}N_5$: C, 65.81; H, 4.67; N, 29.52%; found: C, 65.52; H, 4.93; N, 29.65%.

***N*-(1-(2,2,2-Trifluoroethyl)-1*H*-pyrazol-4-yl)pyridin-2-amine (1′d).** Procedure **A**, except that 150 ^oC and 1.5 hrs was adopted. Light yellow solid, 76%, mp 87.9-88.9 ^oC; ^1H NMR (400 MHz, DMSO): δ 8.92 (s, 1H), 8.15 (s, 1H), 8.10 - 8.11 (m, 1H), 7.54 (s, 1H), 7.44 - 7.49 (m, 1H), 6.66 - 6.68 (m, 1H), 6.60 - 6.63 (m, 1H), 5.02 - 5.09 (m, 2H); ^{13}C NMR (100 MHz, DMSO): δ 155.7, 147.9, 137.3, 132.2, 125.4, 120.9, 113.5, 109.9, 51.8; LC-MS (ESI) = 243.0 $[M+1]^+$. Calcd for $C_{10}H_9F_3N_4$: C, 49.59; H, 3.75; N, 23.13%; found: C, 49.21; H, 3.98; N, 23.01%.

5-Methyl-*N*-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)pyridin-2-amine (1′e). Procedure **A**, except that 150 ^oC and 1.5 hrs was adopted. Gray solid, 81%, mp 96.3-97.5^oC; ^1H NMR (400 MHz, DMSO): δ 9.34 (s, 1H), 8.12 (s, 1H), 7.94 – 8.01 (m, 1H), 7.42 (dd, *J* 8.5, 2.4Hz, 1H), 6.79 (d, *J* 8.4Hz, 1H), 5.14 - 5.23 (m, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 152.4, 146.8, 139.1, 133.4, 133.0, 124.4, 111.2, 110.4, 51.8, 17.5; LC-MS (ESI) = 256.9 $[M+1]^+$. Calcd for $C_{11}H_{11}F_3N_4$: C, 51.56; H, 4.33; N, 21.87%; found: C, 51.13; H, 4.61; N, 21.95%.

5-Cyano-*N*-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)pyridin-2-amine (1′f). Procedure **A**, except that 150 ^oC and 1.5hrs was adopted. Gray solid, 88%, mp 169.2-170.1^oC; ^1H NMR (400 MHz, DMSO): δ 9.84 (s, 1H), 8.59 (s, 1H), 8.23 (s, 1H), 7.80 – 7.96 (m, 1H), 7.70 (d, *J* 0.7Hz, 1H), 6.82 (d, *J* 8.8Hz, 1H), 5.12 – 5.21 (m, 2H); ^{13}C NMR (100 MHz, DMSO): δ 157.1, 153.4, 139.5, 133.0, 123.7, 122.4, 119.1, 110.2, 96.9, 51.9; LC-MS (ESI) = 267.9 $[M+1]^+$. Calcd for $C_{11}H_8F_3N_5$: C, 49.44; H, 3.02; N, 26.21%; found: C, 49.11; H, 3.26; N, 26.12%.

5-Fluoro-*N*-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)pyridin-2-amine (1′g). Procedure **A**, except that 150 ^oC and 1.5hrs was adopted. Gray solid, 83%, mp 102.2-103.3 ^oC; ^1H NMR (400 MHz, DMSO): δ 8.98 (s, 1H), 8.13 (s, 1H), 8.07 - 8.08 (m, 1H), 7.56 (s, 1H), 7.43 – 7.52 (m, 1H), 6.71 - 6.74 (m, 1H), 5.03 - 5.10 (m, 2H); ^{13}C NMR (100 MHz, DMSO): δ 154.6, 152.7, 134.0, 133.8, 132.2, 125.9, 125.7, 125.5, 120.7, 110.8, 51.9; LC-MS (ESI) = 261.1 $[M+1]^+$. Calcd for $C_{10}H_8F_4N_4$: C, 46.16; H, 3.10; N, 21.53%; found: C, 46.01; H, 3.28; N, 21.45%.

5-Nitro-*N*-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)pyridin-2-amine (1′h). Procedure **A**, except that 150 ^{o}C and 1.5hrs was adopted. Gray solid, 63%, mp 181.2-182.3 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 9.06 (s, 1H), 8.29 (s, 1H), 8.27 – 8.23 (m, 1H), 7.75 (s, 1H), 6.81 - 6.83 (m, 1H), 5.12 – 5.20 (m, 2H); ^{13}C NMR (100 MHz, DMSO): δ 158.4, 146.8, 135.9, 132.9, 132.5, 132.2, 125.6, 123.5, 122.8, 52.3; LC-MS (ESI) = 287.9 $[M+1]^{+}$. Calculated for $C_{10}H_8F_3N_5O_2$: C, 41.82; H, 2.81; N, 24.39%; found: C, 41.65; H, 2.93; N, 24.23%.

4-Methyl-*N*-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)pyrimidin-2-amine (1′i). Procedure **A**, earthy yellow solid, 80%, mp 158.2-159.1 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 9.37 (s, 1H), 8.24 (d, *J* 4.9Hz, 1H), 8.07 (s, 1H), 7.61 (s, 1H), 6.60 (d, *J* 5.0Hz, 1H), 4.99 - 5.06 (m, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 167.9, 159.7, 158.1, 132.4, 124.7, 122.8, 121.3, 111.3, 51.8, 24.1; LC-MS (ESI) = 257.9 $[M+1]^{+}$. Calcd for $C_{10}H_{10}F_3N_5$: C, 46.70; H, 3.92; N, 27.23%; found: C, 46.43; H, 4.05; N, 27.31%.

5-Methyl-*N*-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)pyrimidin-2-amine (1′j). Procedure **A,** Gray solid, 77%, mp 186.1-186.7^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 9.29 (s, 1H), 8.25 (s, 2H), 8.04 (s, 1H), 7.58 (s, 1H), 5.02 (q, *J* 9.1Hz, 2H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 158.4, 158.3, 132.3, 125.6, 124.9, 122.8, 120.9, 120.0, 52.0, 14.6; LC-MS (ESI) = 257.9 $[M+1]^{+}$. Calcd for $C_{10}H_{10}F_3N_5$: C, 46.70; H, 3.92; N, 27.23%; found: C, 46.47; H, 4.05; N, 27.02%.

5-Methyl-*N*-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)pyrazin-2-amine (1′k). Procedure **A,** except that 150 ^{o}C and 1.5 hrs was adopted. Earthy yellow solid, 68%, mp 120.8-121.3 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 9.24 (s, 1H), 8.10 (s, 1H), 8.01 (s, 1H), 7.95 (s, 1H), 7.56 (s, 1H), 5.00 - 5.06 (m, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 150.2, 140.7, 140.3, 133.1, 132.3, 125.5, 124.6, 120.9, 52.2, 20.1; LC-MS (ESI) = 258.0 $[M+1]^{+}$. Calcd for $C_{10}H_{10}F_3N_5$: C, 46.70; H, 3.92; N, 27.23%; found: C, 46.54; H, 4.03; N, 27.01%.

***N*-(1-Phenyl-1*H*-pyrazol-4-yl)quinazolin-2-amine (1′l).** The reaction of 1-phenyl-1*H*-pyrazol-4-amine with 2-chloroquinazoline under procedure **A** generated **1'l** as an earthy yellow solid with 75% yield. mp 190.1-191.0 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 9.92 (s, 1H), 9.24 (s, 1H), 8.84 (s, 1H), 7.94 (s, 1H), 7.79 - 7.88 (m, 4H), 7.47 - 7.50 (m, 2H), 7.24 – 7.33 (m, 3H); ^{13}C NMR (100 MHz, DMSO): δ 162.7, 156.8, 151.6, 140.4, 134.7, 133.7, 129.9, 129.4, 128.9, 128.3, 126.1, 126.0, 125.0, 123.6, 120.5, 118.3, 116.6; LC-MS (ESI) = 288.0 $[M+1]^{+}$. Calcd for $C_{17}H_{13}N_5$: C, 71.06; H, 4.56; N, 24.37%; found: C, 70.75; H, 4.67; N, 24.21%.

***N*-(1-(6-Methoxypyridin-3-yl)-1*H*-pyrazol-4-yl)quinazolin-2-amine (1′m).** The reduction of 2-methoxy-5-(4-nitro-1*H*-pyrazol-1-yl)pyridine (0.44 g, 2.0mmol) with H_2 under Pd/C catalysis gave similar 2-methoxy-5-(4-amino-1*H*- pyrazol-1-yl)pyridine as a gray solid (LC-MS (ESI) = 191.0 $[M+1]^{+}$), which underwent the same reaction with 2-chloroquinazoline under procedure **A** generated **1′m** as yellow solid with 66% yield. mp 184.4-184.9 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 9.90 (s, 1H), 9.24 (s, 1H), 8.80 (s, 1H), 8.64 (d, *J* 2.8Hz, 1H), 8.15 – 8.25 (m, 1H), 7.91 (s, 1H), 7.87 (d, *J* 8.0Hz, 1H), 7.78 (d, *J* 6.8Hz, 2H), 7.33 (t, *J* 7.6Hz, 1H), 6.95 (d, *J* 8.9Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 162.7, 161.9, 156.8, 151.6, 136.8, 134.7, 133.6, 132.1, 130.6, 128.3, 126.2, 125.9, 123.6, 120.5, 117.1, 111.4, 53.9; LC-MS (ESI) = 318.8 $[M+1]^{+}$. Calcd for $C_{17}H_{14}N_6O$: C, 64.14; H, 4.43; N, 26.40%; found: C, 64.01; H, 4.52; N, 26.23%.

2-(1-Methyl-1*H*-pyrazol-4-yl)pyrimidine (1′n). Procedure B. White solid, 77%, mp 99.3-101.3 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 8.70 (d, *J* 4.9Hz, 2H), 8.33 (s, 1H), 8.00 (s, 1H), 7.21 (t, *J* 4.9Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 161.1, 157.9, 139.1, 129.2, 122.8,118.8, 39.9; LC-MS (ESI) = 161.0 $[M+1]^{+}$. Calcd for $C_8H_8N_4$: C, 59.99; H, 5.03; N, 34.98 %; found: C, 59.55; H, 5.11; N, 34.65%.

***N*-Methyl-*N*-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)pyridin-2-amine (1′o)** was obtained from the methylation of **1′d**. To anhydrous THF (10mL) was added **1′d** (0.24 g, 1.0 mmol) and NaH (0.05 g, 1.2 mmol) under ice-water bath. The reaction mixture was kept for 0.5 hr, and then methyl iodide (0.17 g, 1.2 mmol) was added. The resultant reaction mixture was warmed to room temperature and kept overnight. The reaction mixture was poured into ice-water, and extracted with ethyl acetate. The combined organic phase was successfully washed with water and brine for three times and dried over Na_2SO_4. After the removal of the solvent, the desired product **1′o** was obtained as light yellow oil with 94% yield. ^{1}H NMR (400 MHz, DMSO): δ 8.17 – 8.18 (m, 1H), 8.07 (s, 1H), 7.72 (s, 1H), 7.49 – 7.53 (m, 1H), 6.68 - 6.71 (m, 2H), 5.07 - 5.14 (m, 2H), 3.33 (s, 3H).^{13}C NMR (100 MHz, DMSO): δ 157.9, 147.8, 137.7, 136.2, 129.9, 126.3, 122.7, 113.7, 107.9, 52.3, 38.4; LC-MS (ESI) = 257.0 $[M+1]^{+}$. Calcd for $C_{11}H_{11}F_3N_4$: C, 51.56; H, 4.33; N, 21.87%; found: C, 51.12; H, 4.71; N, 21.61%.

***N*-Phenyl-1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-amine (1′p). Procedure D.** Brown solid, 46%, mp 137.3-139.1^{o}C; ^{1}H MR (400 MHz, DMSO): δ 7.75 (s, 1H), 7.65 (s, 1H), 7.46 (s, 1H), 7.10 - 7.14 (m, 2H), 6.76 - 6.78 (m, 2H), 6.63 (t, *J* 7.3Hz, 1H), 4.99 - 5.06 (q, *J* 9.1Hz, 2H); ^{13}C NMR (100 MHz, DMSO): δ 146.4, 134.9, 129.7, 129.5, 126.6, 122.8, 121.1, 117.8, 113.5, 52.2. LC-MS (ESI) = 242.0 $[M+1]^{+}$. Calcd for $C_{11}H_{10}F_3N_3$: C, 54.77; H, 4.18; N, 17.42%; found: C, 54.31; H, 4.45; N, 17.14%.

6-Nitro-*N*-[1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl]pyridin-3-amine (1′q). Procedure C. Yellow solid, 73%, mp 96.5-98.3^{o}C; ^{1}H MR (400 MHz, DMSO): δ 9.40 (s, 1H), 8.14 (d, *J* 9.1Hz, 1H), 8.04 (d, *J* 2.8Hz, 1H), 8.01 (s, 1H), 7.67 (d, *J* 0.5Hz, 1H), 7.25 (dd, *J* 9.1, 2.9Hz, 1H), 5.09 (q, *J* 9.1Hz, 2H); ^{13}C NMR (100 MHz, DMSO): δ 147.8, 147.4, 135.6, 134.1, 125.4, 125.2, 123.3, 121.2, 119.2, 52.3; LC-MS (ESI) = 287.9 $[M+1]^{+}$. Calcd for $C_{10}H_8F_3N_5O_2$: C, 41.82; H, 2.81; N, 24.39%; found: C, 41.46; H, 2.90; N, 24.20%.

2-[(1-Methyl-1*H*-pyrazol-4-yl)methyl]pyridine (1′r). Procedure D. Except that, pyrazole (4.5 mmol, 1.5 eq), $Pd(PPh_3)_4$ (0.3mmol, 1.0 eq) and K_2CO_3 (9 mmol) employed. Elution with dichloromethane/ MeOH = 0~5:1. White solid, 46%, mp 107.8-108.3 ^{o}C; ^{1}H NMR (400 MHz, CD_3OD): δ 8.42 - 8.43 (m, 1H), 7.70 - 7.74 (m, 1H), 7.41 (s, 1H), 7.32 (s, 1H), 7.27 - 7.32 (m, 1H), 7.21 - 7.24 (m, 1H), 3.95 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 160.6, 148.2, 138.3, 137.5, 129.7, 123.1, 121.6, 118.8, 37.3, 32.4; LC-MS (ESI) = 174.0 $[M+1]^{+}$. Calcd for $C_{10}H_{11}N_3$: C, 69.34; H, 6.40; N, 24.26%; found: C, 68.93; H, 6.37; N, 24.01%.

3,4-Dimethoxy-*N*-[1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl]benzamide (1′s). Procedure E. White solid, 93%, mp 215.8-216.3 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 10.33 (s, 1H), 8.18 (s, 1H), 7.70 (s, 1H), 7.56 (d, *J* 8.4Hz, 1H), 7.51 (s, 1H), 7.05 (d, *J* 8.4Hz, 1H), 5.07 - 5.14 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 163.7, 151.9, 148.8, 132.7, 126.6,

123.3, 121.2, 111.4, 111.2, 56.1, 56.1, 51.8; LC-MS (ESI) = 329.9 $[M+1]^+$. Calcd for $C_{14}H_{14}F_3N_3O_3$: C, 51.07; H, 4.29; N, 12.76%; found: C, 50.62; H, 4.63; N, 12.63%.

2-Chloro-5-(1-methyl-1*H*-pyrazol-4-yl)pyrimidine (1′t). Procedure B. White solid, 77%, mp 187.2-188.5 °C (lit.[41] 190 °C); ^{1}H NMR (400 MHz, DMSO): δ 8.98 (s, 2H), 8.32 (s, 1H), 8.03 (s, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 157.3, 156.4, 137.1, 129.4, 126.5, 114.3, 39.9; LC-MS (ESI) = 195.0 $[M+1]^+$. It was in agreement with literature.[41]

2-Methoxy-5-(4-nitro-1*H*-pyrazol-1-yl)pyridine (1′u). Procedure F. White solid, 69%, mp 193.8-195.1 °C, ^{1}H NMR (400 MHz, DMSO): δ 9.53 (s, 1H), 8.69 (d, *J* 2.6Hz, 1H), 8.51 (s, 1H), 8.20 (dd, *J* 9.0Hz, 2.8, 1H), 6.99 (d, *J* 9.0Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 163.5, 138.9, 137.4, 132.0, 130.5, 128.8, 111.6, 54.2. LC-MS (ESI) = 221.0 $[M+1]^+$; Calcd for $C_9H_8N_4O_3$: C, 49.09; H, 3.66; N, 25.45%; found: C, 48.85; H, 3.71; N, 25.33%.

4-Nitro-1-phenyl-1*H*-pyrazole (1′v), procedure **F,** white solid, 79%, mp 177.3-178.4 °C, (lit.[42] 128 – 129 °C); ^{1}H NMR (400 MHz, DMSO): δ 9.64 (s, 1H), 8.55 (s, 1H), 7.95 - 7.97 (m, 2H), 7.56 - 7.60 (m, 2H), 7.44 - 7.48 (m, 1H); ^{13}C NMR (100 MHz, DMSO): δ 137.3, 130.8, 130.1, 129.5, 128.7, 128.7, 128.5, 126.3, 119.9. LC-MS (ESI) = 190.0 $[M+1]^+$. It was in agreement with literature.[42]

2-(Pyridin-2-yl)benzonitrile (2a). Colorless oil, 72%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, *J* 4.3, 1H), 7.68-7.77 (m, 4H), 7.57-7.61 (m, 1H), 7.38-7.43 (m, 1H), 7.24-7.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 148.9, 142.5, 135.8, 133.1, 131.8, 129.0, 127.7, 122.3, 122.2, 117.6, 110.1; LC-MS (ESI) = 181.0 $[M+H]^+$. It was in agreement with literature.[17]

5-Chloro-2-(pyridin-2-yl)benzonitrile (2b). Milk white solid, 69%, mp 166-167 °C (lit.[19] 165-166 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, *J* 4.3 Hz, 1H), 7.73-7.78 (m, 4H), 7.56-7.58 (m, 1H), 7.30-7.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1, 149.0, 141.0, 135.9, 133.9, 132.6, 132.1, 130.3, 128.5, 116.4, 111.4; LC-MS (ESI) = 214.9 $[M+H]^+$. It was in agreement with literature.[19]

4-Methyl-2-(pyridin-2-yl)benzonitrile (2c). Light yellow solid, 44%, mp 55-56 °C (lit.[19] 54-55 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.83 (m, 2H), 7.51-7.66 (m, 3H), 7.23-7.32 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.9, 142.4, 133.0, 131.3 , 129.0, 128.6, 20.8; 44%; LC-MS (ESI) = 195.0 $[M+H]^+$. It was in agreement with literature.[19]

A mixture of **2-(pyridin-2-yl)-1-naphthonitrile (2da)** and **3-(pyridin-2-yl)-2-naphthonitrile (2db)**; **2da.** Milk white solid, mp 121-124 °C, (lit.[43] 119.5-123 °C). 37%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77 (s, 1H), 8.33 (d, *J* 8.5 Hz, 1H), 8.08 (d, *J* 8.5 Hz, 1H), 7.86-7.89 (m, 3H), 7.80-7.84 (m, 1H), 7.64-7.68 (m, 1H), 7.55-7.59 (m, 1H), 7.31-7.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 149.9, 143.5, 136.9, 133.1, 133.0, 132.6, 128.9, 128.4, 127.8, 126.5, 125.9, 124.1, 123.4, 117.3, 108.3; LC-MS (ESI) = 230.9 $[M+H]^+$. It was in agreement with literature.[20]

2db, milk white solid, mp 147-148 °C (lit.[19] 146-147 °C) 35%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (d, *J* 4.8 Hz, 1H), 8.38 (s, 1H), 8.28 (s, 1H), 7.91-7.96 (m, 3H), 7.86-7.87 (m, 2H), 7.59-7.66 (m, 2H), 7.34-7.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0 (s, 3H), 155.5, 149.7, 136.9, 136.5, 134.6, 131.7, 129.7, 129.0, 128.5, 128.0, 123.1, 118.9, 108.8; LC-MS (ESI) = 230.9 $[M+H]^+$. It was in agreement with literature.[19]

2-(5-Methylpyrimidin-2-yl)benzonitrile (2e). Milk white solid, 75%, mp 176.3-178.4 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (s, 2H), 8.27 (d, *J* 7.8, 1H), 7.74-7.76 (m, 1H), 7.60-7.62 (m, 1H), 7.45-7.48 (m, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 156.3, 139.6, 133.9, 131.5, 129.1, 128.8, 110.7, 14.6; LC-MS (ESI) = 196.0 $[M+H]^+$. Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52%; found: C, 73.32; H, 4.71; N, 21.33%.

2-(5-Methylpyrimidin-2-yl)-1-naphthonitrile (2f). Milk white solid, 42%, mp 210.6-211.7 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (s, 2H), 8.49 (d, *J* 8.5 Hz, 1H), 8.34 (d, *J* 8.7 Hz, 1H), 8.14 (d, *J* 8.8 Hz, 1H), 7.94 (d, *J* 8.2 Hz, 1H), 7.73 (t, *J* 7.5 Hz, 1H), 7.64 (t, *J* 7.5 Hz, 1H), 3.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 157.5, 140.7, 133.4, 133.3, 132.6, 129.8, 128.8, 128.4, 128.0, 126.3, 126.2, 15.6; LC-MS (ESI) = 245.9 $[M+H]^+$. Calcd for $C_{16}H_{11}N_3$: C, 78.35; H, 4.52; N, 17.13%; found: C, 78.01; H, 4.61; N, 17.01%.

Methyl 6-(4-cyanofuran-3-yl)nicotinate (2g). Milk white solid, 62%, mp 186.3-187.4 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.28 (s, 1H), 8.36-8.38 (m, 1H), 7.86-7.89 (m, 1H), 7.63 (d, *J* 4.0 Hz, 1H), 7.13 (d, *J* 4.0 Hz, 1H), 3.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 151.4, 151.0, 147.6, 138.3, 135.7, 125.8, 124.3, 120.7, 111.1, 52.5; LC-MS (ESI) = 228.9 $[M+H]^+$. Calcd for $C_{12}H_8N_2O_3$: C, 63.16; H, 3.53; N, 12.28%; found: C, 63.01; H, 3.59; N, 12.15%.

1-Methyl-4-(pyrimidin-2-ylamino)-1*H*-pyrazole-5-carbonitrile (3a). Milk-white solid, 82%. mp 149.8-150.6 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 9.77 (s, 1H), 8.44 (d, *J* 4.8 Hz, 2H), 7.74 (s, 1H), 6.84 (t, *J* 4.8 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 159.8, 158.6, 132.4, 129.7, 113.4, 111.6, 107.0, 38.9; LC-MS (ESI) = 200.9 $[M+1]^+$. Calcd for: $C_9H_8N_6$: C, 53.99; H, 4.03; N, 41.98%, found: C, 53.62; H, 4.32; N, 41.72%.

4-(Pyrimidin-2-ylamino)-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole-5-carbonitrile (3b). Milk-white solid, 82%, mp 137.6-138.4 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 10.00 (s, 1H), 8.47 (dd, *J* 4.8, 1.0 Hz, 2H), 7.99 (s, 1H), 6.87 - 6.89 (m, 1H), 5.22 - 5.28 (m, 2H); ^{13}C NMR (100 MHz, DMSO): δ 157.9, 157.8, 130.7, 125.4, 113.6, 108.4, 105.3, 101.6, 50.8; LC-MS (ESI) = 269.0 $[M+1]^+$. Calcd for $C_{10}H_7F_3N_6$: C, 44.78; H, 2.63; N, 31.34%, found: C, 44.57; H, 2.72; N, 31.27%.

1-Phenyl-4-(pyrimidin-2-ylamino)-1*H*-pyrazole-5-carbonitrile (3c). White solid, 84%, mp 180.5-180.9 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 9.99 (s, 1H), 8.48 - 8.50 (m, 2H), 8.17 (s, 1H), 7.67 – 7.69 (m, 2H), 7.56 - 7.60 (m, 2H), 7.47 – 7.51 (m, 1H), 6.88 - 6.90 (m, 1H); ^{13}C NMR (100 MHz, DMSO): δ 159.7, 158.7, 138.8, 135.3, 132.6, 130.1, 129.1, 123.4, 113.7, 111.6, 105.5; LC-MS (ESI) = 263.0 $[M+1]^+$. Calcd for $C_{14}H_{10}N_6$: C, 64.11; H, 3.84; N, 32.04%, found: C, 64.01; H, 3.92; N, 31.79%.

4-(Pyridin-2-ylamino)-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole-5-carbonitrile (3d). Milk-white solid, 77%. mp 136.4-137.3^{o}C; ^{1}H NMR (400 MHz, DMSO): δ 9.50 (s, 1H), 8.20 (s, 1H), 8.15 (d, *J* 4.1 Hz, 1H), 7.55 – 7.62 (m, 1H), 6.88 (d, *J* 8.3 Hz, 1H), 6.76 – 6.81 (m, 1H), 5.20-5.27 (m, 2H); ^{13}C NMR (100 MHz, DMSO): δ 154.5, 147.5, 138.2, 133.6, 132.8, 122.3, 115.7, 111.1, 110.8, 104.7, 51.8; LC-MS (ESI) = 267.9 $[M+1]^+$. Calcd for: $C_{11}H_8F_3N_5$: C, 49.44; H, 3.02; N, 26.21%, found: C, 49.12; H, 3.11; N, 26.01%.

4-(5-Methylpyridin-2-ylamino)-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole-5-carbonitrile (3e). Pale yellow solid, 78%. mp 149.6-151.3 °C; ^{1}H NMR (400 MHz, DMSO): δ 9.34 (s, 1H), 8.12 (s, 1H), 7.97 – 8.12 (m, 1H), 7.42 (dd, *J* 8.5, 2.4 Hz, 1H), 6.79 (d, *J* 8.4 Hz, 1H), 5.14 - 5.21 (m, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 152.4, 146.8, 139.1, 133.4, 133.0, 124.4, 111.2, 110.4, 51.8, 17.5; LC-MS (ESI) = 281.9 $[M+1]^+$. Calcd for $C_{12}H_{10}F_3N_5$: C, 51.25; H, 3.58; N, 24.90%, found: C, 51.01; H, 3.61; N, 24.71%.

4-(5-Cyanopyridin-2-ylamino)-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole-5-carbonitrile (3f). Pale yellow solid, 72%。 mp 188.7-189.4 °C; ^{1}H NMR (400 MHz, DMSO): δ 10.18 (s, 1H), 8.56 (d, *J* 2.2 Hz, 1H), 8.18 (s, 1H), 7.94 (dd, *J* 8.8, 2.3 Hz, 1H), 6.96 (d, *J* 8.8 Hz, 1H), 5.22 - 5.29 (m, 2H); ^{13}C NMR (100 MHz, DMSO) δ 156.6, 152.7, 140.6, 134.6, 131.0, 124.9, 122.2, 118.5, 110.8, 110.4, 106.6, 99.3, 51.9; LC-MS (ESI) = 292.8 $[M+1]^+$. Calcd for $C_{12}H_7F_3N_6$: C, 49.32; H, 2.41; N, 28.76%; found: C, 49.01; H, 2.44; N, 28.65%.

4-(5-Fluoropyridin-2-ylamino)-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole-5-carbonitrile (3g). Pale yellow solid, 77%. mp 157.3-158.3 °C; ^{1}H NMR (400 MHz, DMSO): δ 9.54 (s, 1H), 8.15 (s, 1H), 8.10 (d, *J* 3.0 Hz, 1H), 7.53 - 7.56 (m, 1H), 6.91 (dd, *J* 9.1, 3.7 Hz, 1H), 5.17 - 5.23 (m, 2H); ^{13}C NMR (100 MHz, DMSO): δ 155.7, 153.3, 151.2, 133.9, 133.4, 132.9, 126.5, 125.0, 111.9, 110.9, 104.6, 51.5; LC-MS (ESI) = 285.8 $[M+1]^+$. Calcd for: $C_{11}H_7F_4N_5$: C, 46.32; H, 2.47; N, 24.56%; found: C, 46.09; H, 2.52; N, 24.42%.

4-(5-Nitropyridin-2-ylamino)-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole-5-carbonitrile (3h). Pale yellow solid, 58%. mp 202.7-203.6 °C; ^{1}H NMR (400 MHz, DMSO): δ 8.97 (d, *J* 2.7 Hz, 1H), 8.31 (dd, *J* 9.3, 2.5 Hz, 1H), 8.18 (s, 1H), 7.06 (d, *J* 9.3 Hz, 1H), 5.27 (q, *J* 8.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO): δ 158.1, 145.6, 137.4, 134.9, 133.3, 130.6, 110.6, 110.5, 107.3, 51.7; LC-MS (ESI) = 312.8 $[M+1]^+$. Calcd for $C_{11}H_7F_3N_6O_2$: C, 42.32; H, 2.26; N, 26.92%; found: C, 42.02; H, 2.29; N, 26.69%.

4-(4-Methylpyrimidin-2-ylamino)-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole-5-carbonitrile (3i). Earthy yellow solid, 82%. mp 158.3-159.4 °C; ^{1}H NMR (400 MHz, DMSO): δ 9.92 (s, 1H), 8.35 (d, *J* 4.1, 1H), 7.98 (s, 1H), 6.80 (d, *J* 4.9, 1H), 5.24 - 5.30 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 168.4, 159.2, 158.2, 134.7, 131.1, 125.0, 113.2, 110.9, 107.0, 51.9, 23.8; LC-MS (ESI) = 282.8 $[M+1]^+$. Calcd for $C_{11}H_9F_3N_6$: C, 46.81; H, 3.21; N, 29.78%; found: C, 46.56; H, 3.30; N, 29.67%.

4-(5-Methylpyrimidin-2-ylamino)-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole-5-carbonitrile (3j). Milk white solid, 81%, mp 141.8-143.0 °C; ^{1}H NMR (400 MHz, DMSO): δ 9.89 (s, 1H), 8.36 (s, 2H), 8.01 (s, 1H), 5.24 - 5.31 (m, 2H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 158.3, 157.9, 134.6, 131.4, 125.1, 122.2, 110.9, 106.8, 51.9, 14.7; LC-MS (ESI) = 283.0 $[M+1]^+$. Calcd for: $C_{11}H_9F_3N_6$: C, 46.81; H, 3.21; N, 29.78%; found: C, 46.61; H, 3.32; N, 29.57%.

4-(5-Methylpyrazin-2-ylamino)-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole-5-carbonitrile (3k). Yellow solid, 71%. mp 181.7-182.7 °C; ^{1}H NMR (400 MHz, DMSO): δ 10.06 (s, 1H), 8.29 (s, 1H), 8.17 – 8.19 (m, 1H), 8.06 (s, 1H), 5.25 - 5.31 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 164.5, 157.2, 146.6, 145.8, 131.1, 125.2, 116.3, 107.0, 50.9, 21.6; LC-MS (ESI) =

283.0 $[M+1]^+$. Calcd for: $C_{11}H_9F_3N_6$: C, 46.81; H, 3.21; N, 29.78%, found: C, 46.67; H, 3.29; N, 29.57%.

1-Phenyl-4-(quinazolin-2-ylamino)-1*H*-pyrazole-5-carbonitrile (3l). Yellow solid, 83%, mp 234.9-235.5 ^oC; ^1H NMR (400 MHz, DMSO): δ 10.28 (s, 1H), 9.35 (s, 1H), 8.32 (s, 1H), 7.95 (d, *J* 7.9 Hz, 1H), 7.81 -7.85 (m, 1H), 7.70 – 7.73 (m, 3H), 7.58 - 7.62 (m, 2H), 7.49 - 7.52 (m, 1H), 7.40 - 7.43 (m, 1H); ^{13}C NMR (100 MHz, DMSO): δ 163.3, 156.5, 138.9, 135.2, 134.9, 132.23, 130.0, 129.1, 128.5, 125.9, 124.5, 123.6, 121.1, 112.1, 105.0; LC-MS (ESI) = 312.9 $[M+1]^+$. Calcd for: $C_{18}H_{12}N_6$: C, 69.22; H, 3.87; N, 26.91%, found: C, 69.01; H, 3.95; N, 26.78%.

1-(6-Methoxypyridin-3-yl)-4-(quinazolin-2-ylamino)-1*H*-pyrazole-5-carbonitrile (3m). White solid, 81%, mp 242.3-243.8 ^oC; ^1H NMR (400 MHz, DMSO): δ 10.37 (s, 1H), 9.34 (s, 1H), 8.50 (d, *J* 2.7 Hz, 1H), 8.27 (d, *J* 1.5 Hz, 1H), 8.02 – 8.03 (m, 1H), 7.94 - 7.96 (m, 1H), 7.79 – 7.84 (m, 1H), 7.72 - 7.74 (m, 1H), 7.40 (t, *J* 7.4Hz, 1H), 7.02 - 7.04 (m, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 163.7, 163.3, 156.3, 142.6, 135.8, 134.9, 131.6, 128.5, 125.8, 124.5, 121.1, 111.6, 54.3; LC-MS (ESI) = 343.9 $[M+1]^+$. Calcd for: $C_{18}H_{13}N_7O$: C, 62.97; H, 3.82; N, 28.56%; found: 62.42; H, 3.91; N, 28.47%.

1-Methyl-4-(pyrimidin-2-yl)-1*H*-pyrazole-5-carbonitrile (3n). White solid, 70%, mp 162.3-163.5 ^oC; ^1H NMR (400 MHz, DMSO): δ 8.85 - 8.86 (m, 2H), 8.23 (s, 1H), 7.40 – 7.42 (m, 1H), 4.06 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 158.5, 158.3, 139.2, 128.0, 120.6, 114.9, 111.2, 39.2; LC-MS (ESI) = 185.9 $[M+1]^+$. Calcd for: $C_9H_7N_5$: C, 58.37; H, 3.81; N, 37.82%; found: C, 58.06; H, 3.94; N, 37.77%.

4-[(Methyl)(pyridin-2-yl)amino]-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole-5-carbonitrile (3o). Pale yellow oil, 77%. ^1H NMR (400 MHz, DMSO): δ 8.17 (d, *J* 4.8 Hz, 1H), 7.99 (s, 1H), 7.62 - 7.64 (m, 1H), 6.82 - 6.86 (m, 2H), 5.27 - 5.33 (m, 2H), 3.39 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 156.3, 147.7, 138.5, 136.9, 136.8, 125.0, 122.2, 115.9, 110.5, 108.7, 52.2, 38.5. LC-MS (ESI) = 282.0 $[M+1]^+$; Calcd for $C_{12}H_{10}F_3N_5$: C, 51.25; H, 3.58; N, 24.90%; found: C, 51.01; H, 3.67; N, 24.73%.

4,8-Diphenyl-1,5-bis(2,2,2-trifluoroethyl)-1,4,5,8-tetrahydrodipyrazolo[4,3-*b*:4′,3′-*e*]-pyrazine (4p). LC-MS (ESI) = 480.8 $[M+1]^+$.

1-Ethyl-*N5*-(1-ethyl-1*H*-pyrazol-4-yl)-*N4*,*N5*-bis(6-nitropyridin-3-yl)-1*H*-pyrazole-4,5-diamine (5q). LC-MS (ESI) = 572.8 $[M+1]^+$.

Acknowledgements

Financial support from Hutchison MediPharma (Shanghai) Ltd., the Natural Science Foundation of Henan Province (No. 132300410319), the Research Fund for the Doctoral Program of Higher Education of China (20120101110062); the Natural Science Foundation of China (21376213), and The Low Carbon Fatty Amine Engineering Research Centre of Zhejiang Province (2012E10033) are acknowledged.

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